PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 9/00, 47/18

A1

(11) International Publication Number: WO 96/14829

(43) International Publication Date: 23 May 1996 (23.05.96)

(21) International Application Number: PCT/US95/14910

(22) International Filing Date: 16 November 1995 (16.11.95)

(30) Priority Data:
08/340,763 16 November 1994 (16.11.94) US

(71) Applicant: ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Fort Worth, TX 76134-2099 (US).

(72) Inventors: DESAI, Suketu, Dipakbhai; 7401 Kingswood Drive, Fort Worth, TX 76133 (US). NELMS, Diane, S.; 5604 Wedgmont Circle North, Fort Worth, TX 76133 (US).

(74) Agents: RYAN, Patrick, M. et al.; Alcon Laboratories, Inc., Patent Dept., Q-148, 6201 South Freeway, Fort Worth, TX 76134-2099 (US).

(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PRESERVED OPHTHALMIC DRUG COMPOSITIONS CONTAINING POLYMERIC QUATERNARY AMMONIUM COMPOUNDS

(57) Abstract

Disclosed are storage-stable preserved ophthalmic compositions containing acidic drugs in combination with polymeric quaternary ammonium compounds and boric acid.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CS	Czechoslovakia
CZ	Czech Republic
DE	Germany
DK	Denmark
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgystan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakhstan
LI	Liechtenstein
LK	Sri Lanka
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SI	Slovenia
SK	Slovakia
SN	Senegal
TD	Chad
TG	Togo
TJ	Tajikistan
TT	Trinidad and Tobago
UA	Ukraine
US	United States of America
UZ	Uzbekistan
VN	Viet Nam

PRESERVED OPHTHALMIC DRUG COMPOSITIONS CONTAINING POLYMERIC QUATERNARY AMMONIUM COMPOUNDS

BACKGROUND OF THE INVENTION

The present invention relates generally to ophthalmic compositions. In particular, the present invention relates to the use of a polymeric quaternary ammonium compound and boric acid to provide preserved, storage-stable ophthalmic compositions of acidic drugs.

Ophthalmic formulations generally contain one or more active compounds along with excipients such as surfactants, comforting agents, complexing agents, stabilizers, buffering systems, chelating agents, viscosity agents or gelling polymers and anti-oxidants. Ophthalmic formulations which are intended for multidose use require a preservative.

Organo-mercurials have been used as preservatives in ophthalmic formulations including ophthalmic solutions of acidic drugs. These organo-mercurials include thimerosal, phenylmercuric acetate and phenylmercuric nitrate. Organo-mercurials, however, have limitations due to potential mercury toxicity and poor chemical stability.

Sorbic acid, has also been used to preserve ophthalmic formulations, but it too possesses poor chemical stability as well as poor antimicrobial activity.

Benzalkonium chloride is a widely used preservative in ophthalmic solutions. However, benzalkonium chloride and other quaternary ammonium compounds are generally considered to be incompatible with ophthalmic compositions of drugs with acidic groups, such as nonsteroidal antiinflammatory drugs ("NSAIDS"). These preservative lose their ability to function as they form complexes with the charged drug compounds.

U.S. Patent No. 5,110,493 discloses stable ophthalmic NSAID formulations which do not contain organo-mercurial preservatives. Instead, the reference NSAID formulations use quaternary ammonium compounds, such as cetyltrimethylammonium bromide, cetylpyridinium chloride and preferably, benzalkonium chloride, and a stabilizing amount of a nonionic surfactant.

PCT application WO 94/15597 discloses the use of lauralkonium chloride, the C_{12} homolog of benzalkonium chloride, in ophthalmic formulations of drugs which are incompatible with benzalkonium chloride. Unlike the mixture of alkyldimethylbenzylammonium chloride known as benzalkonium chloride, this PCT application discloses that lauralkonium chloride is compatible with acidic drug entities; apparently it does not form insoluble ion complexes with the charged drug compounds.

In some cases, the present lack of a single preservative which is safe, stable, and able to meet both the United States Pharmacopoeia (USP) and European Pharmacopoeia (Ph.Eur.) preservative effectiveness requirements for ophthalmic formulations of acidic drugs has forced pharmaceutical companies to develop more than one formulation of the same drug, with each formulation containing a different preservative.

U.S. Patent No. 4,960,799 discloses storage stable aqueous ophthalmic compositions containing diclofenac, a nonsteroidal antiinflammatory drug, and/or its pharmaceutically acceptable salts. The reference compositions include EDTA as a stabilizing agent, a solubilizer such as polyethoxylated castor oil, and a bacteriostat. The preferred bacteriostats are thimerosal and sorbic acid. No mention is made of any polymeric quaternary ammonium preservative.

The use of Polyquad® and other polymeric quaternary ammonium compounds as a disinfectant and preservative in contact lens care and artificial tear solutions is known. See, for example, U.S. Patent Nos. 5,037,647; 4,525,346; and 4,407,791. None of these references disclose the use of a polymeric quaternary ammonium compound as a preservative in any formulations of ophthalmic drugs.

SUMMARY OF THE INVENTION

It has now been discovered that the use of a combination of a polymeric quaternary ammonium compound such as Polyquad® and boric acid in ophthalmic compositions of acidic drugs provides a storage-stable composition which has surprisingly good preservative efficacy. This preservative combination of a polymeric quaternary ammonium compound and boric acid is useful in ophthalmic compositions of acidic drugs such as prostaglandins,

antifungals, antibacterials, and diagnostic agents. This preservative combination is especially useful in ophthalmic solutions of drugs containing either a carboxyl group such as non-steroidal anti-inflammatory drugs (NSAIDS) or a sulfonamide group such as antibacterial drugs.

The present invention also relates to a method for treating or controlling ocular inflammation which comprises topically administering to the affected eye a composition comprising a NSAID, a polymeric quaternary ammonium compound and boric acid.

Among other factors, the present invention is based on the discovery that ophthalmic compositions containing a polymeric quaternary ammonium compound and boric acid may be effectively preserved by the USP and Ph.Eur. preservative effectiveness requirements despite the absence of EDTA, a conventional chelating agent known to potentiate the antimicrobial activity of preservatives such as benzalkonium chloride and sorbic acid.

DETAILED DESCRIPTION OF THE INVENTION

The polymeric quaternary ammonium compounds useful in the compositions of the present invention are those which have an antimicrobial effect and which are ophthalmically acceptable. Preferred compounds of this type are described in US Patents Nos. 3,931,319; 4,027,020; 4,407,791; 4,525,346; 4,836,986; 5,037,647 and 5,300,287; and PCT application WO 91/09523 (Dziabo et al.). The most preferred polymeric ammonium compound is polyquaternium-1, otherwise known as Polyquad® or Onamer M®, with a number average molecular weight between 2,000 to 30,000. Preferably, the number average molecular weight is between 3,000 to 14,000.

The polymeric quaternary ammonium compounds are generally used in the compositions of the present invention in an amount from about 0.00001 to about 3 wt%, preferably from about 0.001 to about 0.1 wt%. Most preferably, the compositions of the present invention contain from about 0.001 to about 0.05 wt% of polymeric quaternary ammonium compounds.

The boric acid used in the compositions of the present invention includes not only boric acid, but also its ophthalmically acceptable acid addition salts, as well as borate-polyol complexes of the type described in US Patent No.

5,342,620 (Chowhan). In general, an amount from about 0.3 to about 5.0 wt% is used in the compositions of the present invention. It is preferred to use from about 0.3 to about 3.0 wt%, and it most preferred to use from about 0.5 to about 2.0 wt%. The water soluble borate-polyol complexes useful in the compositions of the present invention preferably comprise borate and polyol in a molar ratio between about 1:1 and about 1:10.

Suitable ophthalmic agents which may be included in the compositions of the present invention and administered via the method of the present invention include, but are not limited to, the racemic and enantiomeric forms and ophthalmically acceptable salts, amides, esters and prodrugs of the following types of drugs containing an acidic functionality such as -COOH, $-SO_2NH_2$, or SO_2NHR groups: anti-glaucoma agents, such as carbonic anhydrase inhibitors, prostaglandins and prostaglandin derivatives; non-steroidal anti-inflammatory agents, including but not limited to those classified as aryl- or heteroaryl-alkanoic acids, such as diclofenac, bromfenac, flurbiprofen, suprofen, ketorolac, indomethacin and ketoprofen; anti-bacterials and anti-infectives, including sulfa drugs, such as sulfacetamide sodium, and beta-lactams such as penicillins and cephalosporins; and diagnostic agents such as sodium fluorescein. Combinations of ophthalmic agents may also be used in the compositions of the present invention.

The compositions of the present invention may additionally include other ophthalmically acceptable components such as comfort enhancing agents, buffers (e.g., phosphate, acetate, carbonate, and citrate), other preservatives (e.g., benzalkonium chloride and individual homologs of benzalkonium chloride, parabens, chlorobutanol, and biguanides such as chlorhexidine and hydroxypropyl methyl biguanide), surfactants (e.g. poloxamers such as Pluronics®; polysorbates such as Tweens®; tyloxapol; sarcosinates such as Hamposyl®; and polyethoxylated castor oils such as Cremophor®), and tonicity agents (e.g., sodium chloride, mannitol, dextrose and xylitol). In addition, other excipients, such as antioxidants, chelating agents and complexing agents may be added to the compositions of the present invention as desired or as necessary.

The compositions of the present invention may also include viscosity modifying agents such as: cellulosic ethers, such as, hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), ethyl hydroxyethyl cellulose,

hydroxypropyl cellulose, methyl cellulose, and carboxymethyl cellulose; carbomers (e.g. Carbopol®); polyvinyl alcohol; polyvinyl pyrrolidone; alginates; carrageenans; and guar, karaya, agarose, locust bean, tragacanth and xanthan gums. The concentration of such viscosity modifiers will vary between about 0.1 to about 5 wt%, but such formulations will generally have a viscosity between about 10 and about 5000 centipoise.

The ophthalmic compositions of the present invention may additionally contain polymers which will undergo sol-to-gel transition upon exposure to physical or chemical stimuli, such as changes in pH, ion concentration, and/or temperature. Examples of such polymers include but are not limited to: certain carrageenans, and gellan, locust and xanthan gums, such as those described in US Serial No. 08/108,824 (Lang et al.), US 4,861,760 (Mazuel et al), US 4,136,173 (Pramoda et al), US 4,136,177 (Lin et al.), and US 4,136,178 (Lin et al). The contents of these patent applications and patents relating to the polymers cited above are hereby incorporated by reference herein.

The acidic drugs in the compositions of the present invention may also be encapsulated in microparticles such as microcapsules, microspheres, nanocapsule, nanospheres, and liposomes to improve comfort, and/or provide for sustained release.

The following examples are presented to illustrate further various aspects of the present invention, but are not intended to limit the scope of the invention in any respect.

EXAMPLE 1

The following formulations are representative of preferred compositions of the present invention.

Ingredient	Formulation (wt%)		
	A	B	C
Sodium Diclofenac	0.1	---	---
Sulfacetamide Sodium	---	10	---
Suprofen	---	---	0.25
HPMC*	0.1	0.1	0.1
Tromethamine	2.0	2.0	2.0
Boric Acid	1.2	1.2	1.2
Vitamin E TPGS**	3.0	3.0	3.0
Mannitol	3.5	1.6	3.6
Polyquad®	0.005	0.005	0.005
HCl/NaOH	q.s. to pH 7.4	q.s. to pH 7.4	q.s. to pH 7.4
Purified Water	q.s. to 100%	q.s. to 100%	q.s. to 100%

* Hydroxypropyl Methyl Cellulose

** Vitamin E Tocopheryl Polyethylene Glycol 1000 Succinate

Preparation:

The preparation of Formulation A is detailed below. Formulations B and C can be prepared in similar fashion.

Initially, a 10% stock solution of TPGS and a 2% stock solution of HPMC were prepared in water under constant stirring. Heat was applied if necessary to ensure complete dissolution.

To a tared glass vessel containing approximately 40 % final weight of purified water was added diclofenac-sodium. This mixture was stirred until the diclofenac was completely dissolved. The following ingredients were then added with stirring in the order given below, and each ingredient was completely dissolved before addition of the next ingredient: stock solution of vitamin E TPGS; tromethamine; boric acid; Polyquad®; mannitol; and stock solution of HPMC.

Water was then added to bring the formulation to 95% of its final weight, and the pH of the formulation adjusted to between 7 and 7.4 using NaOH and/or HCl. Water was then added to bring the final weight to 100%. The resulting formulations were approximately isotonic (above 300 milliOsmoles per kilogram (mOsm/kg)).

EXAMPLE 2

The antimicrobial preservative effectiveness of the polymeric quaternary ammonium compound/boric acid combination of the present invention was determined using an organism challenge test according to the methods described in the United States Pharmacopeia (USP) and European Pharmacopoeia (Ph.Eur.). Samples were inoculated with known levels of gram-positive (*Staphylococcus aureus* ATCC 6538) and gram-negative (*Pseudomonas aeruginosa* ATCC 9027 and *Escherichia coli* ATCC 8739) vegetative bacteria, yeast (*Candida albicans* ATCC 10231) and mold (*Aspergillus niger* ATCC 16404) and sampled at specified intervals to determine if the antimicrobial preservative system was capable of killing or inhibiting the propagation of organisms purposely introduced into the formulation. The rate or level of antimicrobial activity determined compliance with the USP and/or Ph.Eur. preservative efficacy standards for ophthalmic preparations.

The compendial preservative standards for ophthalmic preparations are presented below:

For Bacteria:

	Log Reduction of Organism Population		
Time Pull	USP	Ph.Eur. A (Target)	Ph.Eur. B (Min)
6 hours	-	2	-
24 hours	-	3	1
7 days	-	-	3
14 days	3	-	-
28 days	NI	NR	NI

For Fungi:

Time Pull	USP	Ph.Eur. A (Target)	Ph.Eur. B (Min)
7 days	-	2	-
14 days	NI	-	1
28 days	NI	NI	NI

NR = No organisms recovered
NI = No increase at this or any following time pulls
\- = No requirement at this time pull

The results of the preservative challenge study conducted on Formulation A are shown below in Table 1. These results illustrate that an ophthalmic formulation of an acidic drug can be globally preserved, that is, can comply with the USP and Ph.Eur. A preservative effectiveness requirements for ophthalmic preparations, using a combination of a polymeric quaternary ammonium compound and boric acid.

Table 1

Preservative Challenge Results for Formulation A

TEST ORGANISM	INITIAL COUNT	Number of Microorganisms Per Milliliter*					
		6 Hr	24 Hr	Day 7	Day 14	Day 21	Day 28
S. aureus	1.5×10^6	<10	<10	<10	<10	<10	<10
P. aeruginosa	1.0×10^6	<10	<10	<10	<10	<10	<10
E. coli	1.1×10^6	<10	<10	<10	<10	<10	<10
C. albicans	1.2×10^6	6.3×10^5	4.1×10^4	4.4×10^2	<10	<10	<10
A. niger	1.3×10^6	1.4×10^6	3.9×10^4	2.5×10^2	8.0×10^1	6.5×10^1	<10

*Limit of detection: <10 CFU/mL

The invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

WHAT IS CLAIMED IS:

1. A preserved storage stable ophthalmic composition comprising a therapeutically effective amount of one or more acidic ophthalmic agents, a preservative-effective amount of a combination of an antimicrobial polymeric quaternary ammonium compound and boric acid, and an ophthalmically acceptable vehicle.

2. The composition of Claim 1 wherein the acidic ophthalmic agent is selected from the group consisting of anti-glaucoma, non-steroidal anti-inflammatory, anti-bacterial, anti-infective and diagnostic agents.

3. The composition of Claim 2 wherein the ophthalmic agent is a non-steroidal anti-inflammatory agent.

4. The composition of Claim 3 wherein the non-steroidal anti-inflammatory agent comprises an aryl- or heteroaryl-alkanoic acid, or an ophthalmically acceptable salt, ester, amide, or prodrug thereof.

5. The composition of Claim 4 wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of: diclofenac, flurbiprofen, suprofen, bromfenac, keterolac, indomethacin, ketaprofen, and ophthalmically acceptable salts, esters, amides or prodrugs thereof.

6. The composition of Claim 5 wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of diclofenac and its ophthalmically acceptable salts, esters, amides, or prodrugs thereof.

7. The composition of Claim 5 wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of suprofen and its ophthalmically acceptable salts, esters, amides, or prodrugs thereof.

8. The composition of Claim 5 wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of bromfenac and its ophthalmically acceptable salts, esters, amides, or prodrugs thereof.

9. The composition of Claim 8 wherein the antimicrobial polymeric quaternary ammonium compound is polyquaternium-1.

10. The composition of Claim 9 wherein the polyquaternium-1 has a number average molecular weight from 2,000 to 30,000.

11. The composition of Claim 10 wherein the polyquaternium-1 has a number average molecular weight from 3,000 to 14,000.

12. The composition of Claim 1 wherein the concentration of the antimicrobial polymeric quaternary ammonium compound is between about 0.00001 and about 3 percent by weight.

13. The composition of Claim 12 wherein the concentration of the antimicrobial polymeric quaternary ammonium compound is between about 0.001 and about 0.1 percent by weight.

14. The composition of Claim 13 wherein the concentration of the antimicrobial polymeric quaternary ammonium compound is between about 0.001 and about 0.05 percent by weight.

15. The composition of Claim 1 wherein the ophthalmically active forms of boric acid are selected from the group consisting of boric acid, ophthalmically acceptable acid addition salts of boric acid and borate-polyol complexes.

16. The composition of Claim 1 wherein the concentration of boric acid is between about 0.3 and about 6 percent by weight.

17. The composition of Claim 16 wherein the concentration of boric acid or ophthalmically active forms thereof is between about 0.3 and about 3 percent by weight.

18. The composition of Claim 17 wherein the concentration of boric acid or ophthalmically active forms thereof is between about 0.5 and about 2 percent by weight.

19. The composition of Claim 15 wherein the ophthalmically active forms of boric acid are water soluble borate-polyol complexes having a molar ratio of borate to polyol from 1:1 to 1:10.

20. A method for treating or controlling ocular inflammation, comprising the topical ocular application of the composition of Claim 3.

21. The method of Claim 20, wherein the non-steroidal anti-inflammatory agent comprises an aryl- or heteroaryl- alkanoic acid, or an ophthalmically acceptable salt, ester, amide or prodrug thereof.

22. The method of Claim 21 wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of diclofenac and its ophthalmically acceptable salts, esters, amides or prodrugs.

23. The method of Claim 21 wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of suprofen and its ophthalmically acceptable salts, esters, amides or prodrugs.

24. The method of Claim 21 wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of bromfenac and its ophthalmically acceptable salts, esters, amides or prodrugs.

25. A globally preserved ophthalmic formulation comprising diclofenac or an ophthalmically acceptable salt, ester, amide or prodrug thereof, and which meets USP and Ph.Eur. preservative effectiveness requirements using a combination of an antimicrobial polymeric quaternary ammonium compound and boric acid.

26. The formulation of Claim 25 wherein the formulation comprises sodium diclofenac, hydroxypropylmethyl cellulose, tromethamine, boric acid, mannitol, Polyquad® and a comfort-enhancing agent.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 95/14910

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00 A61K47/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 306 984 (SYNTEX INC.,U.S.A.) 15 March 1989 cited in the application see the whole document ---	1-26
A	WO,A,94 15597 (ALLERGAN INC.,U.S.A.) 21 July 1994 cited in the application see the whole document ---	1-26
A	US,A,4 960 799 (I.E.NAGY) 2 October 1990 cited in the application see the whole document ---	1-26

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 March 1996	22.03.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Scarponi, U

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 95/14910

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 076 136 (ALCON LABORATORIES INC.,U.S.A.) 6 April 1983 cited in the application see the whole document see claims see examples	1-26

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US95/14910

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 20-24 are directed to a method of treatment of the human/animal body by therapy (Rule 39.1 (iv) PCT), the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inte ·onal Application No
PCT/US 95/14910

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-306984	15-03-89	AU-B-	2204288	16-03-89
		CA-A-	1328614	19-04-94
		DE-A-	3870111	21-05-92
		FI-B-	94924	15-08-95
		IE-B-	60717	10-08-94
		JP-A-	1104023	21-04-89
		JP-B-	6096542	30-11-94
		NO-B-	175404	04-07-94
		US-A-	5414011	09-05-95
		US-A-	5110493	05-05-92
WO-A-9415597	21-07-94	AU-B-	6021794	15-08-94
US-A-4960799	02-10-90	NONE		
EP-A-76136	06-04-83	US-A-	4407791	04-10-83
		AU-B-	557817	08-01-87
		AU-B-	9050382	08-04-83
		CA-A-	1194421	01-10-85
		WO-A-	8301003	31-03-83
		US-A-	4525346	25-06-85